

REMARKS

Reconsideration of this application is respectfully requested.

Previously, the pending claims were 569-595, 597-643, 645-646, 648-651, 654-679, 681-682, 684-687, 690-714, 716-717, 719-747, 749-797, 800-803, 806-831, 833-834, 836-839, 842-866, 868-869, 871-899, 901-947, 949-950, 952-955, 958-983, 985-986, 988-991, 994-1018, 1020-1021, 1023-1051, 1053-1099, 1101-1102, 1104-1107, 1110-1135, 1137-1138, 1140-1143, 1146-1173, 1175-1250, 1252-1253, 1255-1258, 1260-1294, 1296-1407, 1409-1568, 1570-1612 and 1614-1748. Replacement claims 1728, 1732-1733, 1738-1739 and 1743 have been entered above. New claims 1749-1766 have also been added. No claims have been canceled. Accordingly, the claims now pending are 569-595, 597-643, 645-646, 648-651, 654-679, 681-682, 684-687, 690-714, 716-717, 719-747, 749-797, 800-803, 806-831, 833-834, 836-839, 842-866, 868-869, 871-899, 901-947, 949-950, 952-955, 958-983, 985-986, 988-991, 994-1018, 1020-1021, 1023-1051, 1053-1099, 1101-1102, 1104-1107, 1110-1135, 1137-1138, 1140-1143, 1146-1173, 1175-1250, 1252-1253, 1255-1258, 1260-1294, 1296-1407, 1409-1568, 1570-1612 and 1614-1766.

I. Amendments to Pending Claims

Applicants have effected several amendments to the claims above in an effort to separate sequencing processes from processes in which hybrid formation takes place, such as hybridization-based detection and chromosomal characterization. Applicants have also sought to separate their claimed sequencing processes from processes for preparing labeled oligo- or polynucleotides. Thus, claims 1728, 1732-1733, 1739 and 1743 have been amended.

In further detail, the dependencies in each of claims 1728, 1732, 1733, 1739 and 1743 have been amended so that only claims explicitly directed to sequencing processes are recited therein. Thus, amended claim 1728 now depends from claims 1700, 1701, 1702 and 1704. As amended above, claims 1732 and 1733 both depend from claims 1700, 1701, 1702, 1703 and 1704, thereby automatically separating subsequent dependent claims 1734-1738¹ from Applicants' non-hybridization sequencing processes. Amended claim 1739 now depends from claims 638, 640, 674, 676, 790, 792, 826, 828, 942, 944, 978, 980, 1094, 1096, 1130 and 1132, each of which is explicitly directed to a sequencing process. Finally, claim 1743 depends from claims 569, 721, 873, 1025, 1177, 1700, 1701, 1702, 1703 or 1704. In light of the changes to 1739 and 1743, subsequent dependent claims 1744-1748 have also been separated from Applicants' non-hybridization sequencing processes.

No new matter is believed presented by these amendments since the sole purpose of the foregoing amendments is to establish a line of demarcation between Applicants' claimed sequencing processes and their claimed processes in which hybridization and hybrid formation take place, and other claimed processes for preparing labeled oligo- or polynucleotides.

II. New Claims

By adding new claims 1749-1765 above, Applicants have continued their effort to demarcate subject matter drawn to sequencing processes from hybridization-related processes. Thus, the subject matter recited in each of claims 1749-1765 is related to processes for hybridization-based detection or

¹ A minor word change ("on" to -- with --) has also been made to claim 1738.

chromosomal characterization, or processes for preparing labeled oligo- or polynucleotides.

Claims 1749-1756 are directed to embodiments of the chelation processes that are not sequencing processes. The subject matter of claims 1749-1756 mimics that in other pending claims already of record. See, e.g., claims 1728-1729 and claims 1733-1738. In further detail, new claim 1749 depends from claims 1706, 1708, 1709, 1710 or 1711, and it recites "wherein in said providing step, the chelating compounds or chelating components provide a detectable signal that is radioactive, chromogenic, fluorogenic, fluorescent, chemiluminescent, electron dense or magnetic." Claim 1750 depends from claims 1705, 1706, 1707, 1708, 1709, 1710 or 1711, and it recites "wherein said detecting step is carried out by a compound or component that is radioactive, chromogenic, fluorogenic, fluorescent, chemiluminescent, electron dense or magnetic." Claim 1751 is similarly worded. This claim depends from claims 1705, 1706, 1707, 1708, 1709, 1710 or 1711 and recites "wherein in said detecting step, the chelating compounds or chelating components have chelated a metal or metal ion selected from the group consisting of heavy metals and rare earth metals." In new claim 1752, which depends from claim 1751, that "heavy metal comprises cobalt."

New claim 1753 depends from the process of claim 1750 and it contains the language "wherein said detecting step is carried out radioactively." Claim 1754 depends from claim 1753, and it recites "wherein said radioactive detection is carried out by means of an isotope." In claim 1755, that isotope is "a β or γ emitter." New claim 1756 recites that the "radioactive detection is carried out with an isotope selected from the group consisting of bismuth-206, bismuth-207, cobalt-60, gadolinium-153, strontium-90 and yttrium-90."

New claims 1757-1759 are directed to embodiments of the detectable non-radioactive moieties recited in various detection, chromosomal characterization or labeled oligo- or polynucleotide preparation claims. To a large extent, claims 1757-1759 correspond to the subject matter in pending claims 1739-1741, already of record. Claim 1757 depends from claims 1354, 1356, 1450, 1452, 1512, 1514, 1652 or 1654, and it recites "wherein said fluorescent aromatic or cycloaliphatic group comprises a fluorescent dye." Claim 1758 depends from claims 1373 or 1671, and it contains the language "wherein said non-radioactively modified or labeled nucleotides or nucleotide analogs are labeled with the same indicator molecules." In claim 1759, also dependent from claims 1373 or 1671, the "non-radioactively modified or labeled nucleotides or nucleotide analogs are labeled with different indicator molecules."

New claims 1760-1765 provide embodiments for the analog recitation in Applicants' claimed processes for hybridization-based detection and chromosomal characterization, and for labeled oligo- or polynucleotide preparation. Nevertheless, these claims mimic the language in pending sequencing claims, namely, claims 1743-1748. Thus, claim 1760 is directed to base analogs selected from the group consisting of "analogs of pyrimidine, purine and 7-deazapurine." In claim 1761, the purine analogs can be selected from the group consisting of "thymidine analogs, uridine analogs, deoxyuridine analogs, cytidine analogs and deoxycytidine analogs." In claim 1762, the aforementioned uridine analogs comprise "5-bromo-2'-deoxyuridine-5'-phosphate." In claim 1763, the deoxycytidine analogs comprise "5-hydroxymethyl-2'-deoxycytidylic acid." In claim 1764, the purine analogs are defined as being selected from the group consisting of "adenosine analogs, deoxyadenosine analogs, guanosine analogs and deoxyguanosine analogs." The adenosine analogs are defined in claim 1765 as being selected from the group consisting of "tuberacidin and toyocamycin."

As in the case of pending claims 1743-1748, the subject matter of claims 1760-1765 is similarly supported by Applicants' original disclosure.

Finally, new claim 1766 has been added. Modeled on pending claim 569, new claim 1766 is directed to a process for determining the sequence of a nucleic acid of interest.² Three steps are recited in claim 1766. The first step calls for "providing or generating detectable non-radioactively labeled nucleic acid fragments, each fragment comprising a sequence complementary to said nucleic acid of interest or to a portion thereof, wherein each of said fragments comprises one or more detectable non-radioactively modified or labeled nucleotides or nucleotide analogs, which nucleotide analogs can be attached to or coupled to or incorporated into DNA or RNA." The second step recites "subjecting said detectable non-radioactively labeled fragments to a sequencing gel to separate or resolve said fragments." The third step calls for "detecting non-radioactively the presence of each of said separated or resolved fragments by means of said detectable non-radioactively modified or labeled nucleotides or nucleotide analogs, and determining the sequence of said nucleic acid of interest."

Support for claim 1766³ is found variously in the originally filed specification. On page 84, second paragraph, it is disclosed:

This type of self-signaling molecule can be used to monitor any nucleic acid hybridization reaction. It is particularly important for detecting nucleic acids in gels (for example, **sequencing gels**).

The significance of the term "sequencing gels" was also thoroughly addressed in the Declaration of Dr. James J. Donegan In Support of Adequate

² In its first step, pending claim 569 recites "wherein said one or more detectable non-radioactively modified or labeled nucleotides or nucleotide analogs have been modified or labeled on at least one of the sugar moiety, the sugar analog, the phosphate moiety, the phosphate analog, the base moiety, or the base analog thereof." New claim 1766 lacks this recitation.

³ Claim 1766 essentially replaced former claim 329, which was canceled.

Description, that Declaration having been submitted as an exhibit to Applicants' July 6, 1998 Supplemental Amendment. See Donegan Declaration beginning with Paragraph 8 on page 4.

With respect to the nucleotide analogs recited in new claim 1766, this matter was thoroughly addressed in Applicants' May 23, 2000 Amendment Under 37 C.F.R. §1.115. See for example, page 187, last paragraph, through page 217, first full paragraph, citing as support for "nucleotide analogs et al." the following twenty-six (26) portions of the specification:

Page 1, 10th line from bottom

Page 7, line 9

Page 9, 2nd & 3rd lines from bottom

Page 31, line 4

Page 37, 12th line from bottom

Page 54, 2nd & 3rd full paragraphs

Page 54, last paragraph

Page 60, Example X

Page 61, Examples XI and XII

Page 62, Example XIII

Page 63, Examples XIV & XV

Page 64, Examples XVI & XVII

Page 66, Example XIX

Page 71, Example XXIII

Page 72, Examples XXIV & XXV

Page 75, Example XXXI

Page 76, Example XXXII

Page 78, Example XXXV

Page 79, Example XXXVII

Page 80, Example XXXVIII

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Original claims 71, 72, 73, 75 & 76

In the May 23, 2001 Amendment, the following twelve (12) portions in the specification were also cited in the specification for supporting "attachment, coupling and incorporation" of nucleotides or nucleotide analogs into DNA or RNA:

Page 12, last paragraph

Page 56, Example IV

Page 57, Example V

Page 58, Example VII

Page 60, Example IX

Page 67, Example XX

Page 71, Example XXIII

Page 77, Example XXXIV

Page 99, 2nd paragraph

Page 101, first paragraph

Original claims 7 & 145

Entry of new claim 1766 is respectfully requested.

As required under the new Simplified Amendment Practice. Replacement paragraphs/sections/claims to be used. 37 CFR 1.121, as set forth in the Changes to the Patent Rules (37 CFR 1.121 MPEP Bookmark, Volume 1, Issue 3), a marked-up version of the claims amended above is attached as Exhibit 1. This marked-up version is titled "Version With Markings To Show Changes Made."

In addition, Applicants are submitting a clean version of all pending claims following implementation of the claim changes in this paper, including the claim amendments and the addition of new claims 1749-1766. Attached as Exhibit 2,

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-- December 21, 2001)

this clean consolidated claim set is being submitted pursuant to the Changes to the
Patent Rules, Volume 1, Issue 3, October 20, 2000.

Favorable action on this application is respectfully requested.

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SUMMARY AND CONCLUSIONS

As amended and added above, claims 569-595, 597-643, 645-646, 648-651, 654-679, 681-682, 684-687, 690-714, 716-717, 719-747, 749-797, 800-803, 806-831, 833-834, 836-839, 842-866, 868-869, 871-899, 901-947, 949-950, 952-955, 958-983, 985-986, 988-991, 994-1018, 1020-1021, 1023-1051, 1053-1099, 1101-1102, 1104-1107, 1110-1135, 1137-1138, 1140-1143, 1146-1173, 1175-1250, 1252-1253, 1255-1258, 1260-1294, 1296-1407, 1409-1568, 1570-1612 and 1614-1766 are being presented for further prosecution on the merits.

The fee for adding new independent claim 1766 and new dependent claims 1749-1765 is \$570 (1 new independent claims @ \$84 = \$84 and 27 new dependent claims @\$18 = \$486). The United States Patent and Trademark Office is hereby authorized to charge the amount of \$570 to Deposit Account No. 05-1135. No other fee or fees are believed due in connection with this Second Supplemental Amendment. In the event that any such other fee or fees are due, however, authorization is hereby given to charge the amount of any such fee or fees to Deposit Account No. 05-1135, or to credit any overpayment thereto.

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If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that he be contacted at the number provided below.

Respectfully submitted,



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MARKED-UP VERSION OF THE AMENDED CLAIMS

Exhibit 1 [Second Supplemental Amendment And Consolidation Amendment
(Following Applicants' November 20, 2001 Consolidation Amendment
- December 21, 2001)]

1728. (Twice Amended) The process of any of claims 1700, 1701, 1702[~~;~~] or 1704, [~~1706, 1708, 1709, 1710 or 1711,~~] wherein in said providing step, the chelating compounds or chelating components provide a detectable signal that is radioactive, chromogenic, fluorogenic, fluorescent, chemiluminescent, electron dense or magnetic.

1732. (Twice Amended) The process of any of claims 1700, 1701, 1702, 1703[~~;~~] or 1704, [~~1705, 1706, 1707, 1708, 1709, 1710 or 1711,~~] wherein said detecting step is carried out by a compound or component that is radioactive, chromogenic, fluorogenic, fluorescent, chemiluminescent, electron dense or magnetic.

1733. (Amended) The process of any of claims 1700, 1701, 1702, 1703[~~;~~] or 1704, [~~1705, 1706, 1707, 1708, 1709, 1710 or 1711,~~] wherein in said detecting step, the chelating compounds or chelating components have chelated a metal or metal ion selected from the group consisting of heavy metals and rare earth metals.

1738. (Amended) The process of claim 1735, wherein said radioactive detection is carried out [~~on~~] with an isotope selected from the group consisting of bismuth-206, bismuth-207, cobalt-60, gadolinium-153, strontium-90 and yttrium-90.

1739. (Amended) The process of any of claims 638, 640, 674, 676, 790, 792, 826, 828, 942, 944, 978, 980, 1094, 1096, 1130 or 1132, wherein said fluorescent aromatic or cycloaliphatic group comprises a fluorescent dye.

Filed: June 7, 1995

Marked-Up Version Of The Amended Claims

Page 2 [Exhibit 1 To Second Supplemental Amendment

And Consolidated Amendment -- December 21, 2001]

1743. (Amended) The process of any of claims 569, 721, 873, 1025, 1177,
[~~1298, 1473, 1474, 1475, 1476, 1582,~~] 1700, 1701, 1702, 1703[~~;~~] or 1704,
[~~1705, 1706, 1707, 1708, 1709, 1710, 1711 and 1712,~~] wherein said base
analog is selected from the group consisting of analogs of pyrimidine, purine and
7-deazapurine.

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